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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/048,197	01/23/2002	Joelle Thonnard	BM45399	2955

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EXAMINER
BASKAR, PADMAVATHI

ART UNIT	PAPER NUMBER
1645	15

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No. 10/048,197	Applicant(s) THONNARD, JOELLE	
	Examiner Padmavathi v Baskar	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27, 29, 32, 34, 35, 38, 43 - 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27, 29, 32, 34,, 38, 43 - 44* is/are rejected.

7)☒ Claim(s) *35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/24/03 has been entered.

2. The amendment filed on 6/24/03 has been entered into the record. Claims 27, 29, 32, 34, 35, 38, 43 - 44 are pending in the application.

Information Disclosure Statement

3. Information Disclosure Statement filed on *6/24/03* (Paper # 14) is acknowledged and a signed copy is attached to this Office action.

Claim Rejections - 35 USC 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying

5. Claims 27, 29, 32, 34, 38 and 43-44 are rejected under 35 U.5.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the interim guidelines on written description published June 15, 1998 in the Federal Register at

Volume 63, Number 114, pp 32639-32645 (also available at www.uspto.gov). This is a written description rejection.

The claims are drawn to an isolated polypeptide comprising SEQ.ID.NO: 2 and an immunogenic fragment comprising at least 15 amino acids or 20 amino acids. Claims are also drawn to fusion protein and immunogenic compostion comprising said fragments, pharmaceutically acceptable carrier and adjuvant.

The specification broadly describes as part of the invention, an isolated protein of SEQ ID NO: 2, which is encoded by BASB122 gene from M.catarrhalis, strain Mc2931 (ATCC 43617). The specification also teaches on page 66 that this full-length protein contains 111 amino acids. . However, the specification does not teach fragments or immunogenic composition or fusion protein comprising fragments of 15 amino acids or 20 amino acids of SEQ.ID.NO: 2

The actual biological function of the protein represented as SEQ ID NO: 2 is not set forth in this specification. Applicants broadly describe the invention as embracing any deletion by use of language in which a specified percent of amino acids can be changed in the protein. USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116).

Thus, an isolated polypeptide consisting of SEQ ID NO: 2 meets the written description provision of 35 U.S.C. 112, first paragraph for the reasons set forth below.

The specification fails to teach an isolated polypeptide fragment of 15 amino acids or 20 amino acids of SEQ.ID.NO: 2 and it is noted that the claimed fragments do not exist as an

independent invention. The actual structure or other relevant identifying characteristics of each protein fragment having the claimed properties of the protein can only be determined empirically by actually making it and determine whether such a fragment has the particularly disclosed properties of full length protein. For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function. This specification does not teach and is devoid of correlation with full length SEQ ID NO: 2 protein and said protein with an undetermined function. There is no written description support for an isolated fragments comprising 15 amino acids or 20 amino acids or immunogenic composition or fusion protein comprising said fragments as claimed.

The isolated polypeptide comprising SEQ ID NO: 2 is uncharacterized by this specification and is not asserted to belong to any known family of proteins (Outer membrane, Transferrin binding protein etc). The specification fails to teach the structure or relevant identifying characteristics of a representative number of SEQ.ID.NO: 2 fragments, sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 U5PQ2d 1601, 1606 (CAFC 1993) and Amgen Inc V Chugai Pharmaceutical Co Ltd., 18 U5PQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 U5PQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

6. Claims 27, 29, 32, 34, 38 and 43-44 are rejected under 35 U.5.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide consisting of the amino acid sequence SEQ ID NO: 2, fusion protein comprising the amino acid sequence SEQ

ID NO: 2 and immunogenic composition comprising the amino acid sequence SEQ ID NO: 2 does not reasonably provide enablement for an isolated polypeptide comprising fragments of at least 15 or 20 amino acids of SEQ ID NO: 2, fusion protein and immunogenic composition comprising fragments of at least 15 or 20 amino acids of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches the production of recombinant BASB 122 encoding a polypeptide comprising 111 amino acids from Moraxella catarrhalis strain Mc 2931 (ATCC 43617). The specification discloses the claimed polypeptide can be used as an immunogen and formulating the compositions in Freund's adjuvant to immunize mice for preparing antibodies. However, the specification fails to teach an isolated polypeptide comprising a fragments of at least 15 or 20 amino acids of SEQ ID NO: 2. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid sequences (i.e. fragments) for different aspects of biological activity cannot be predicted a priori and must be determined empirically on a case-by-case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology,

8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol. 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis in proteins. Such proteins differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition. Applicants have not taught which residues of SEQ ID NO: 2 can be varied and still achieve a polypeptide that is functional and is capable of use as a diagnostic using immunological means of recognition. The specification has not conceived any other functionally equivalent protein fragments and does not set forth the general tolerance to substitutions and where substitutions could be made to get the claimed fragments. Since, the specification lacks a written description of any fragment of SEQ ID NO: 2, it is not enabled for this language because it fails to enable the skilled artisan to envision the detailed chemical structure of the claimed polypeptide fragments of SEQ ID NO: 2 respectively, as well as how to use the polypeptide fragments, one of skill in the art would be unable to produce these fragments. In view of the unpredictability of the art, the lack of teachings of the specification, it would require undue experimentation on the part of the skilled artisan to practice the invention as claimed.

Claim Rejections - 35 USC 112, second paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 27, 29, 32, 34, 35, 38 and 43 - 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 is rejected as being vague and indefinite for the recitation of "matching." As written it is impossible to understand whether applicant is claiming amino acid sequence SEQ.ID.NO: 2 or some other sequence which matches SEQ.ID.NO: 2 anywhere in the sequence.

9. The rejection of claims 27, 29, 32, 34, 38, 43 and 44 under 35 U.S.C. 102(b) as being anticipated by Helminen et al 1994 (J.Infec.Dis, 170; 867-872) is maintained as set forth in the previous office action.

The claims are directed to an isolated polypeptide comprising a member selected from the group consisting of (a) an amino acid sequence matching SEQ.ID.NO: 2 and (b) an immunogenic polypeptide comprising a fragment sequence of at least 15 or 20 amino acids that matches an aligned contiguous segment of SEQ.ID.NO: 2 wherein the isolated polypeptide, when administered with a carrier induces an antibody or T-cell mediated immune response to a polypeptide having the SEQ.ID.NO: 2. The claims are also drawn to a fusion protein comprising said isolated polypeptide and an immunogenic composition comprising said isolated polypeptide in a pharmaceutically acceptable carrier. The immunogenic composition further comprises one other Moraxella antigen.

Helminen et al, 1994, disclose outer membrane proteins i.e., OMPs prepared from *M.catarrhalis* cells by EDTA buffer method. Monoclonal antibodies were produced by immunizing mice (page 868, left column under production of Mabs) with OMPs. Applicant's use of the open-ended term "comprising " in claim 61 fails to exclude unrecited steps or ingredients and leaves the claims open for inclusion of unspecified ingredients, even in major amounts. Therefore, the claims read on the disclosed isolated polypeptide, OMPs from *M.catarrhalis*. As OMPs comprise many proteins together it would read on fusion protein comprising said peptides and one other Moraxella antigen. Since monoclonal antibodies were raised against OMPS by immunizing the mice with OMPs in a buffer, the examiner considers the OMPs in a buffer as an immunogenic composition comprising said polypeptide in a pharmaceutically acceptable carrier. Therefore, the claimed polypeptides, fusion proteins and immunogenic compositions as claimed are inherent in the preparation of OMPs. See In re Horvitz, 168 F 2d 522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948). In the absence of evidence to the contrary the disclosed prior art OMPs read on the claimed invention. Since the Office does not have the facilities for examining and comparing applicants' claimed isolated polypeptide comprising SEQ.ID.NO: 2 with the OMPs of prior art, the burden is on applicant to

show a novel or unobvious difference between the claimed product and the product of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicants' arguments filed on 6/25/03 have been fully considered but they are not deemed to be persuasive.

Applicant states that applicant's invention is directed to BASB122 polypeptides and immunogenic fragments thereof. Further, it is stated that later published paper by Aebi et al (Infection and Immunity 1997, 65; 4367-77) concurrently submitted as Exhibit A discloses the deduced amino acid sequences for the UspA1 and UspA2 genes. The two disclosed proteins are said to be reactive to the monoclonal antibody disclosed in Helminen et al, 1994. The proteins have accession numbers AAB 96359 (UspA1) and AAB 96391 UspA2), and PubMed sequences viewer printouts are submitted as Exhibit B. Applicant states that the disclosed sequences have no significant similarity to the claimed SEQ.ID.NO: 2 from the disclosed UspA1 and UspA2.

Applicant's use of BASB 122 for an isolated polypeptide comprising SEQ.ID.NO: 2 is merely a lab designation and does not contain any other characteristics to differentiate from other proteins known in the art of Moraxella.

Applicant states that the two disclosed proteins UspA1 and UspA2 by Aebi et al in Exhibit A are reactive to monoclonal antibody 17C7 and these proteins have no significant similarity with the claimed invention because the sequences submitted in exhibit B are different from the claimed isolated polypeptide SEQ.ID.NO: 2. However, it is the position of the examiner that the amino acid sequence of SEQ.ID.NO: 2 of the claimed invention has not been shown to bind to 17C7 or not, or even to convalescent sera from Moraxella infected individuals. Therefore, comparing with another Moraxella polypeptide based on binding to one monoclonal antibody 17C7 does not provide enough evidence to indicate that the claimed polypeptide is different.

It is noted that the monoclonal antibody 17C7 used by Helminen et al, 1994 et al is reactive to a high molecular weight protein around 300 KD (see Figure 1B, 2 and 3) and at the same time the same antibody binds to 88 KD, UspA 1 protein and 66KD, UspA2 protein in Exhibit A (Aebi et al 1997). This indicates that the binding of an antibody depends on the conformational epitope of a protein and configuration present on antibody molecule links with a corresponding antigenic determinant of a protein and not on the entire protein. However, the claimed polypeptide has not been shown to bind to any antibody. Therefore, the epitope to which the antibody binds is not clear in applicant's invention. Therefore, the exhibits did not provide any evidence to over come the rejection of record.

The examiner did not reject claim 35, which is drawn to an isolated polypeptide consisting of SEQ.ID.NO: 2. However, the examiner rejected the claims drawn to an isolated polypeptide comprising SEQ.ID.NO: 2, based on inherency since the outer membranes of Helminen et al, 1994 contain several proteins including an isolated polypeptide comprising SEQ.ID.NO: 2, UspA 1, UspA2, Tbp1 and Tbp2 etc. Therefore, the claimed polypeptide contains more than 111 amino acids. The use of open-ended term "comprising in the claims fails to exclude unrecited steps or ingredients and leaves the claims open for inclusion of unspecified ingredients, even in major amounts See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594. Therefore, this rejection is maintained

Objection

10. Claim 35 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Status of Claims

11. Claims 27, 29, 32, 34, 38 and 43-44 are rejected.

Claim 35 is objected.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma Baskar whose telephone number is (703) 308-8886. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4 PM EST

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Padma Baskar Ph.D.

8/14/03

LYNETTE R. F. SMITH
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